Title: COMPARATIVE HEMODYNAMIC EFFECTS OF D-TUBOCURARINE AND METOCURINE IN THE DOG

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Introduction. D-tubocurarine, because of its histamine releasing and ganglionic blocking properties is known to have significant hemodynamic effects. Structure activity relations predict that methylation to produce the bisquaternary metocurine would result in a compound which produces less histamine release, less profound ganglionic blockage, and thus a lesser degree of hemodynamic side effects. This study was undertaken to compare in equipotent doses the hemodynamic effects in dogs of metocurine and d-tubocurarine.

Methods. Ten mongrel dogs weighing between 17 and 25 kg were studied utilizing chloralose(100mg/kg)and morphine (1mg/kg) anesthesia. Central venous, pulmonary arterial and pulmonary capillary wedge pressures were recorded via catheters introduced into the right external jugular, and arterial pressure in the abdominal aorta via a catheter introduced through the left femoral artery. Heart rate was measured by a tacograph and cardiac output by dye dilution technique. Muscle paralysis was measured by twitch response of the right tibilis anterior muscle via stimulation of the peroneal nerve. Ventilation was controlled to maintain end-tidal CO_2 at 3.5-4%. After steady state control measurements had been obtained, the animals were arbitrarily divided into two groups. Group I animals received d-tubocurarine at three dosage levels 0.35,0.7 and 1.4 mg/kg. Group II animals received metocurine at doses of 0.2,0.4 and 0.8 mg/kg. Complete recovery was allowed between each dose. Following administration of each dose measurements were made at 2,5,10 and 20 minutes. The following parameters were measured or calculated: mean BP,CVP,PA,PCW, cardiac output, systemic and pulmonary vascular resistance, heart rate and stroke volume.

Results. Table I d-Tubocurarine

	.35 mg/kg		.7 mg/kg		1.4 mg/kg	
	Control	2min	Control	2min	Control	2min
HR beat/min	57 ±6	138 ±13^{x}	72 ±9	135 ±9^{x}	70 ±6	142^{+} ±14
BP mmHg	118 ±7	76 ±12^{x}	117 ±8	54^{+} ±13	114 ±9	55^{x} ±17
C.O. L/min	2.48 ±0.5	2.6 ±0.9	2.2 ±0.4	1.3 ±0.9	2.4 ±0.4	1.8 ±0.8
CVP mmHg	4.7 ±0.3	1.3^{+} ±0.2	5 ±0.7	1.8^{x} ±0.6	4.6 ±0.7	2^{+} ±0.5
$\overline{PA}$ mmHg	12 ±0.3	11 ±0.7	13 ±1.6	11^{x} ±1.6	18 ±1	13 ±2.7
$\overline{PCW}$ mmHg	5.5 ±0.4	2 ±0.4	6.0 ±0.9	2.5^{+} ±0.6	5.6 ±0.7	2.6^{x} ±0.7
SVR units	55 ±8	40^{x} ±8	63 ±10	35^{x} ±5	52 ±10	34 ±4
PVR units	3.1 ±0.6	5.4^{x} ±1.5	3.9 ±1.0	8.5^{x} ±2.3	6.1 ±1.2	8.4 ±2.6

x = p<0.05; + = p<0.01 (both tables)

Table II Metocurine

	0.2 mg/kg		0.4 mg/kg		0.8 mg/kg	
	Control	2min	Control	2min	Control	2min
H.R. beat/min	64 ±7	74 ±8	68 ±9	83^{x} ±6	63 ±8	120^{+} ±13
BP mmHg	108 ±4	107 ±5	98 ±6	91 ±10	106 ±25	83^{x} ±9
C.O. L/min	2.4 ±0.3	2.8 ±0.8	2.9 ±0.6	3.2 ±0.5	2.3 ±0.2	2.9^{x} ±0.4
CVP mmHg	3.8 ±0.7	3.5 ±0.7	3.5 ±0.4	2.7^{x} ±0.4	4.5 ±0.8	2.5^{x} ±0.4
$\overline{PA}$ mmHg	14 ±1	14 ±1	15 ±1.7	15 ±1.7	15.5 ±1	14 ±1.8
$\overline{PCW}$ mmHg	6.7 ±1	6.2 ±1	6.3 ±0.5	5.8 ±0.7	6.8 ±0.7	4^{x} ±1.1
SVR units	48 ±6	42 ±6	39 ±8	33^{x} ±6	47 ±5	33^{+} ±6
PVR units	3.4 ±0.7	3.2 ±0.7	3.7 ±1.3	3.5 ±1.2	4.1 ±0.5	4.1 ±0.6

In Group I (d-tubocurarine) significant increase in heart rate occurred with each dose at 2 minutes. In addition, mean BP fell with each dose and was statistically significant with 0.7 and 1.4 mg/kg respectively. The cardiac output did not change significantly and pulmonary vascular resistance rose. In Group II (metocurine) no significant changes occurred throughout the study with doses of 0.2 mg/kg. Only with 0.4 mg/kg and 0.8 mg/kg were significant changes noted, and only with the highest dose were these changes comparable to those produced by d-tubocurarine at the lowest dose.

Discussion. The dosage of d-tubocurarine utilized in this study represents the ED_{95} for neuromuscular blockade in the dog(0.35mg/kg) and 2 and 4 times ED_{95} respectively. It is apparent that at all dose levels significant hemodynamic changes occurred within two minutes of administration. The dose levels of metocurine utilized represent twice the ED_{95}(0.2mg/kg) 4 and 8 times ED_{95} respectively. Thus only at 8 times ED_{95} did metocurine produce hemodynamic changes similar to those observed with d-tubocurarine at ED_{95}. These data demonstrate that the safety margin for hemodynamic changes after metocurine in the dog is therfore 8 times greater than that of d-tubocurarine. Since metocurine does not block the cardiac muscarinic receptors, it will not produce a tachycardia until histamine release occurs. These data suggest that significantly higher doses of d-tubocurine are required. In addition, metocurine has a weaker ganglionic blocking action. These data would support the concept that metocurine may be the relaxant of choice in the management of patients where these hemodynamic changes must be avoided, i.e., patients with significant coronary artery disease.